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Appellant(s): Jones et al.

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Julia E. Abers
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed April 9, 1992.

(1) Status of claims.

The statement of the status of claims contained in the brief is correct.

(2) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) Summary of invention.

The summary of invention contained in the brief is correct.

(4) Issues.

(5) Grouping of claims.

The brief includes a statement that claims do not stand or fall together but fails to present reasons in support thereof. Therefore, these claims are presumed to stand or fall together.

(6) Claims appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) Prior Art of record.

4,683,195	Mullis et al.	7-1987
4,883,750	Whiteley et al.	11-1989
0246864	Carr et al.	11-1987
8909835	Orgel	10-1989
0336731	Wallace	10-1989

(8) New prior art.

No new prior art has been applied in this examiner's answer.

(9) Grounds of rejection.

The following ground(s) of rejection are applicable to the appealed claims.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that

the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Mullis et al in view of Carr and Whiteley et al.

Mullis et al teach a method of amplifying a contiguous fragment of nucleic acids involving creating a single stranded nucleic acid (ss DNA); creating a complementary strand; denaturing the newly formed complementary strand from the original nucleic acid sequence; repeating the process whereby now the original single stranded DNA and the newly formed complementary strand are each used to form a new set of duplexes. This process occurs one or more times and Mullis et al point out the great value of repeating the process a large number of times since it results in a geometric amplification of the duplex. Mullis et al form the complementary strand using a polymerase enzyme while applicants form the complementary strand by ligating fragments together; however, one of ordinary skill in the art would have know that a complementary strand could be formed by ligating smaller fragments together.

Carr et al and Whiteley et al teach that a complementary strand can be formed by ligating fragments together either with

a ligase (Carr et al and Whiteley et al) or by use of a polymerase (Carr et al). One of ordinary skill in the art would have known that what was important was the formation of the complementary sequence and that whether one used short fragments (amplification probes) or DNA and a polymerase or short fragments of DNA and a ligase with or without a polymerase that the only thing of importance would be the formation of a complementary strand which could be used in subsequent reactions. Examiner notes that the phosphate ester linkage, catalyzed by ligase occurs by chemically reacting a hydroxyl group with a phosphate group. Thus, the invention as claimed would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Carr and Whiteley et al in view of Mullis et al.

Carr et al and Whiteley et al teach an assay method which entails: utilizing an initial template and hybridizing two fragments to it. Ligating those fragments together and denaturing the fragments. They do not iterate the process to obtain an amplification product and they do not use both strands of the initial template. Mullis et al teach the importance and value of using both strands and an iterative procedure in order to amplify the target sequence. The method of modification of the primary references to obtain an amplification product would have been obvious in light of the teachings of Mullis et al. Thus, the invention as claimed would have been obvious to one of

ordinary skill in the art at the time the invention was made.

(11) Response to argument.

Appellants argue that their method allows the blunt-end by-product to form and discriminates the non-target-derived blunt-end ligated product from the desired target derived amplification product. They argue that with their detection system, incorrectly aligned spurious blunt-end ligated amplification by-product cannot act as a template for hybridization of the detection probes. As a result, the detection product serves as an indication of only the correctly assembled amplification product, nearly all of which is traceable to product.

Examiner contents that appellants' argument is not convincing because the above statement seems to imply that one can quantitatively determine how much target existed in the original sample. However, the argument appears to be faulty because if the correctly aligned spurious blunt-end ligated amplification by-product (low copy number) was formed early in the cycling and subsequent exponential amplification occurred there would be just as much if not more product produced from target-independent ligated by-product than from original target of interest.

Appellants argue that some of the claims include a detection step and that somehow this should confer patentability on the invention. Examiner is not convinced: all of the applied references use and describe a detection step. Even the titles point this out: Mullis et al. "Process for amplifying, detecting, and/or cloning nucleic acid sequences"; Whiteley et al.

"Detection of specific sequences in nucleic acids"; and while the title of Carr does not specifically recite "detection" the abstract indicates it is a "method of discriminating... and detecting any hybrid obtained". Furthermore, Mullis et al clearly teach the production of a complement and subsequent detection by use of a hybridization probe.

It appears to the examiner that the approach taken by appellants in arguing their position is better suited to claims having a Jepson format wherein the detection method confers an unexpected advantage over the prior art. That is, it appears that appellants argue that what makes their method superior over the combined art is the end detection step. However, applicants have failed in writing their claims in a Jepson format. That is, appellants' detection step may in fact confer an unexpected advantage over the prior art, however, applicants persist in arguing and claiming that the amplification method as well as the detection method is unobvious over the prior art. Also, appellants' claims are not commensurate in scope with their arguments. Appellants argue that each of their detection probes bridge and fully hybridize with the junction of two adjacent amplification probes. However, those claims limited to a detection step actually recite a method wherein only one or a couple of nucleotides per detection probe is complementary the amplification probe due to appellants recitation of "comprising" and "complementary to a portion", and this language wherein detection probes have limited complementarity to amplification probes renders said detection probes indistinguishable from

amplification probes which makes the method read as though the detection may in fact be just another iteration, rather than a detection. Appellants' arguments are not convincing. Upon further consideration examiner has not maintained the rejections under 35 U.S.C. § 112, first paragraph.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

LAS

Laurie Scheiner
July 13, 1992

DAVID L. LACEY
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